can function to stimulate proliferation of mesodermal cells as claimed.

As a preliminary matter, Mosby's Medical Dictionary defines endothelium as follows:

> Endothelium is defined as the layer of simple squamous epithelial cells that lines the heart, the blood and lymph vessels, and the serous cavities of the body. It is highly vascular, heals quickly, and is derived from the mesoderm. *Mosby's Medical Dictionary, 5th Ed. (1998).*

Further, on page 1, lines 16-22 of the specification, applicants explain that vasculogenesis results from the *in situ* differentiation of mesodermal cells. The applicants then add that the sprouting of new capillaries from the pre-existing vasculature is termed angiogenesis. On page 2 lines 14-15, the applicants further explain that angiogenesis involves the maintenance of endothelial cells in the cell cycle. From these teachings it is readily ascertainable that vasculogenesis results from the differentiation of mesodermal cells to endothelial cells and that angiogenesis results from proliferating endothelial cells.

Thus, when the applicants state on p.3, lines 31-33 that VEGF has important regulatory functions in the formation of new blood vessels during embryonic vasculogenesis and angiogenesis during adult life, one of ordinary skill in the art would logically draw the conclusion that the role of VEGF in vasculogenesis is that of a mesodermal not an endothelial cell mitogen (because vasculogenesis results from differentiation of mesodermal cells not endothelial cells, see previous page). Thus, given the role of VEGF as a mesodermal cell mitogen, one of ordinary skill in the art would also be

led to the conclusion that a VEGF analogue such as ORFV2-VEGF would also function as a mesodermal cell mitogen.

Second, noting that ORFV2-VEGF binds to VEGFR-2, the Office action asserts that because VEGFR-2 is expressed on endothelial cells, one of skill in the art would not predict that a ligand for this receptor would have any effect on mesodermal cells.

On this second aspect of the rejection, the examiner's attention is directed to the specification at p.7, lines 31-33 and p.8, lines 1-2 which notes that experiments with homozygous mice with inactivated alleles of VEGFR-2 suggest that VEGFR-2 is required for endothelial cell proliferation, hematopoesis and vasculogenesis. *Shalaby et al., Nature 376:62-66 (1995); Shalaby et al., Cell 89: 981-990 (1997).* More specifically, Shalaby et al. in Nature 376:62-66 states:

> During the early stages of the embryonal development, VEGFR-2 is first expressed in presumptive mesodermal yolk-sac blood island progenitors at 7 days post-coitum and then in the primitive endothelial cells surrounding the blood islands.

These teachings clearly demonstrate that VEGFR-2 is expressed in mesodermal cells. Accordingly, one skilled in the art would readily recognize that ORFV2-VEGF can bind to VEGFR-2 on mesodermal cells.

Third, the Office action asserts that the 87% homology between NZ10 and ORFV2-VEGF is inadequate to indicate to one of skill that NZ10 would function as an agonist (rather than an antagonist) of VEGFR-2 and that one of skill would not be able to use NZ10 as a mitogen or ORFV2-VEGF as a mesodermal cell mitogen with a reasonable expectation of success.

The explanation for the second aspect of the rejection, set forth above, supports the applicants' claim that ORFV2-VEGF is a mesodermal cell mitogen. With respect to the rejection of the applicants' disclosure of NZ10 as an agonist, applicants respectfully note that the Court of Customs and Patent Appeals (CCPA) has held that a teaching in specification "*must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112, *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In re Marzocchi and Horton, 169 USPQ 367, 369 (CCPA 1971) (emphasis added by the court). In the event that doubt does exist, the rejection can be overcome "by suitable proofs indicating that the teaching contained in the specification is truly enabling." Id.

Here, the statement in the specification is objectively true and supported by the "suitable proofs" set forth in the attached Declaration under 37 CFR 1.132. The Declaration substantiates that the mitogenic activity of NZ10 is comparable to the mitogenic activity disclosed in Example 5 for ORFV2-VEGF. From these results, NZ10 is shown to be an agonist, not an antagonist, of VEGFR-2 with mitogenic properties similar to that of ORFV2-VEGF. Accordingly, the teaching in the specification that NZ10 is an agonist of VEGFR-2 is objectively accurate and an enabling disclosure. The Declaration also includes the results of the VEGFR-2 binding assay for NZ10 which was not provided in Example 2.

Fourth, the Office action asserts that activation of VEGFR-2 by ORFV2-VEGF appears to be less effective than activation by VEGF and that the specification does not provide objective evidence to indicate that activation is "specific"

for VEGFR-2 as claimed in claims 5 and 6. The Office action adds that since the evidence does not preclude the existence of other receptors through which ORFV2-VEGF might function, one of skill would not predictably be able to use ORFV2-VEGF for "specific activation" of VEGFR-2 as claimed.

On this matter, the examiner's attention is directed to the specification at p. 11, lines 18-22 which provides as one aspect of the invention, a method for activation of VEGFR-2 which comprises the step of exposing cells bearing said receptor to an effective receptor activating dose of ORFV2-VEGF or NZ10 or a fragment or analog thereof. This aspect of the invention is evidenced in Figure 4A which shows that ORFV2-VEGF precipitates VEGFR-2 but not VEGFR-1 and that ORFV2-VEGF phosphorylates VEGFR-2 but not VEGFR-3. These figures demonstrate that ORFV2-VEGF has a specific binding affinity for VEGF-2. That VEGF has a stronger binding affinity for VEGFR-2 than ORFV2-VEGF is inconsequential in light of the fact that ORFV2-VEGF binds to VEGFR-2 and not VEGFR-1 and VEGFR-3.

Because the specification successfully teaches that ORFV2-VEGF and NZ10 can act as mesodermal cell mitogens, that ORFV2-VEGR can bind to VEGFR-2 on mesodermal cells, and that ORFV2-VEGF has a specific binding affinity for VEGFR-2, applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-7 were rejected under 35 U.S.C. § 112, second paragraph as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following terms were listed as

indefinite: "endothelial or mesodermal cell proliferation stimulating amount" of claims 1-7, "receptor activating dose" of claim 5, and "vascular permeability modulating amount" of claim 7.

Applicant respectfully traverse this rejection and in support, presents the holding of the case In re Halleck, 164 USPQ 647 (1970). In In re Halleck, the CCPA reversed the examiner's rejection of the appealed claims under 35 U.S.C. § 112, second paragraph as too broad. The examiner found the claim language "an effective amount" to be functional and inadequately defined because of an insufficient number of examples to enable determination of proportions of a given agent. Halleck, 164 USPQ at 648. On reversing the rejection, the CCPA held that the functional term "an effective amount...for growth stimulation" is not objectionable where the *amount* as such is not critical and its use has been approved in many cases. Id. at 649 (emphasis added by the court). The CCPA explained that requiring the appellant to ascertain and recite the numerical limits for each agent known would require undue research. The CCPA observed that specifications are written for those skilled in the art and that consequently, those skilled in the art are able to determine from the written disclosure and its examples the dosage of an effective amount for growth stimulation. Id.

Since the applicants' specification sets forth an adequate written description with examples for the skilled artisan to determine the effective doses and amounts to be used, this rejection must be reversed under the principles set forth by the CCPA in In re Halleck.

Rejection under 35 U.S.C. § 103(a)

Claims 1-7 were rejected as obvious over Lyttle et al in view of Thomas. Lyttle et al. teaches ORFV2-VEGF as a VEGF homologue and that supernatants from cells infected with the OV NZ2 virus are mitogenic for vascular endothelial cells. Thomas teaches the use of mammalian VEGF to stimulate proliferation of endothelial cells. The Office action notes that both Lyttle et al. and Thomas fail to teach the use of ORFV2-VEGF to stimulate the proliferation of endothelial cells or the modulation of vascular permeability.

From the Lyttle et al. and Thomas references, the Office action asserts that it would have been obvious to one of ordinary skill in the art to combine the teachings of Lyttle et al. with those of Thomas to substitute ORFV2-VEGF in the method of Thomas to stimulate proliferation of endothelial cells and increase vascular permeability with a reasonable expectation of success because Thomas teaches that VEGF can be used to repair tissue injury and Lyttle et al. teaches ORFV2-VEGF as a VEGF homologue with similar mitogenic effects on endothelial cells.

Applicants respectfully traverse this rejection. The data from Lyttle et al. cited in the Office action derives from unpublished preliminary studies conducted with the supernatants from cells infected with two strains of the orf virus (OV NZ2 and OV NZ7). The discussion hypothesizes on how VEGF activity might be an advantage to the virus and explicitly states that the reason for any observed pathology is not clear. Applicants submit that this unpublished preliminary study does not give rise to a reasonable expectation of success because the experiments are conducted with cell supernatants and not the isolated protein. Because

cell supernatants are a mixture of unknown proteins, it cannot be assumed that VEGF is the mitogenic protein in the cell supernatants. Further, as the Lyttle et al. reference does not provide any experimental procedures or supporting objective data of the binding of the orf virus to the VEGF receptor in the cell supernatants, the results of the preliminary unpublished cell supernatant study should not be relied upon on the grounds that the validity of the study cannot be verified.

As NZ10 was first discovered by the applicants, the non-obviousness of claims 1-7 is clear with respect to NZ10. Furthermore, any comparison between the NZ2 strain analyzed in Lyttle et al. and NZ10 would not be proper because NZ10 may have a different binding specificity than the NZ2 strain analyzed in Lyttle et al. The mere fact that a particular strain of the orf virus shares sequence homology or DNA homology with VEGF provides no additional information on the function of ORFV2-VEGF or NZ10. Indeed, this very fact is acknowledged on p.3 of the Office action with the following statement: "homology is insufficient to imply a similar function or any function at all."

The Thomas reference fails to correct the deficiencies in the Lyttle et al. reference. Specifically, because Lyttle et al. does not teach the use of ORFV2-VEGF to stimulate proliferation of endothelial cells through VEGFR-2 to induce vascular permeability, the teaching in the Thomas reference that VEGF stimulates proliferation of endothelial cells through VEGFR, fails to supply the essential elements of the present invention. Accordingly, the hypothetical combination of Lyttle et al. and Thomas do render the present invention

obvious by teaching each of the claimed elements as necessitated by 35 U.S.C. § 103(a).

Because Lyttle et al. and Thomas fail to teach or suggest, "A method for stimulating proliferation of endothelial or mesodermal cells, comprising the step of exposing said endothelial cells to an effective endothelial or mesodermal cell proliferation stimulating amount of a polypeptide selected from the group of ORFV2-VEGF and NZ10" (claim 1), these prior art references do not render claims 1-7 obvious. Accordingly, applicants respectfully request reconsideration and withdrawal of this prior art rejection.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #1064/44803).

Respectfully submitted,

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